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Radiation Therapy for Recurrent or Residual Pituitary Macroadenoma Invading Extrasellar Structures

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Purpose: This study aimed to evaluate the efficacy of radiation therapy (RT) for recurrent or residual pituitary macroadenoma (PMA) invading extrasellar regions.

Materials and Methods: Patients from 2000 to 2020 who received RT with conventional fractionation for recurrent or residual PMA were included. The patients were divided according to the type of tumor [functioning (fx) or non-fx] and the aim of RT (salvage RT alone, immediate postoperative RT, delayed postoperative RT). Local and biochemical failure-free rates (FFR) were calculated using the Kaplan–Meier method.

Results: With a median follow up of 82 months (IQR; 42–132 months), 36 patients treated with conventional RT (total 45–54 Gy in 1.8 or 2 Gy per fraction) for recurrent or residual PMA were analyzed. The 10-year local FFRs after RT for non-fx and fx tumor were 100% and 74.4%, respectively (p=0.047). In the immediate postoperative RT group, the 10-year local FFR was 100%, which was higher than the 90% FFR for salvage RT alone or 80% FFR for the delayed postoperative RT group (overall p=0.043, immediate vs. salvage; p=0.312, immediate vs. delayed; p=0.072). The local FFR was compared according to size of tumor with a cut-off value of 4 cm, and there was no significant difference (10-year local FFR 100% vs. 84.7% for >4 cm vs. <4 cm, p=0.320). The extents of extrasellar region invasion were not predictive of local failure after RT. We found no grade ≥3 acute toxicities or newly developed visual impairments as a late toxicity of RT.

Conclusion: Conventional RT is safe and effective for the local control of recurrent or residual PMA. Our data suggest that immediate postoperative RT can be beneficial in recurrent or residual PMA, although further studies to evaluate risk factors of treatment failure in terms of treatment and disease characteristics are required.

Key Words: Pituitary macroadenoma, radiation therapy, extrasellar invasion, local failure, biochemical failure

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INTRODUCTION

Pituitary adenomas are a common form of intracranial tumors, accounting for 10% of all adult intracranial neoplasms.[1] Surgical resection with a transsphenoidal approach (TSA) has been the treatment of choice for pituitary adenoma with limited toxicity, with pharmacological therapies also available for functioning (fx) tumors. The treatment objectives for patients with pituitary adenoma are complete resection of the tumor and normalization of hormone hypersecretion, which can be achieved in up to 80% of patients depending on the extent or size of the tumor.[2-4] Radiation therapy (RT) is also an available treatment option and has been reported to have excellent local control rates, especially in non-fx tumors.[5-7] Because it is possible to achieve these treatment objectives in a considerable

proportion of patients with non-aggressive adenoma through surgical resection or pharmaco-therapy, RT is usually considered a secondary or adjuvant treatment option in most cases. Furthermore, late toxicity of RT in the form of hypopituitarism or optic pathway damage discourages clinicians from using RT for benign tumors. However, for tumors with extrasellar invasion, the complete resection rate decreases, and a multimodal approach is required to increase tumor control rates and maintain patient quality of life.

The aggressiveness of pituitary adenoma is generally defined by tumors with a high Ki-67 proliferation index, aggressive histology, and remnant tumor in the extrasellar area, and tumors with those factors are thought to be at risk of local progression. The risk of recurrence in pituitary adenoma after surgical resection has been reported to be approximately 30%–50% at 5–10 years,[8-10] and the rates are much higher for post-surgical remnant tumors (15% of intrasellar remnant tumors, compared to 51% of extrasellar residuals).[11] Current treatment guidelines from the Congress of Neurological Surgeons and the European Society of Endocrinology recommend RT for reducing tumor progression rates in patients with these risk factors.[12,13] Although there are clinical reports that have analyzed treatment outcomes of patients with recurrent or residual pituitary macroadenomas (PMA) invading the extrasellar structure, which is considered to heighten the risk for local recurrence, factors affecting local control rates after RT have not been well investigated yet.

Therefore, the primary aim of this study was to analyze long-term local failure-free rates (FFR) of recurrent or residual PMAs invading extrasellar areas when treated with RT. We also investigated whether differences in local control in these patients could be attributed to RT timing. The incidence of acute and chronic toxicity in patients with recurrent PMA after RT was investigated as the second endpoint of the study.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Severance Hospital (IRB no. 4-2021-1623).

Study population

We investigated patients from 2000 to 2020 who received RT for recurrent or residual PMA after surgical resection. Patients aged <18 years and those without a minimum of 1 year of follow-up were excluded. After additional exclusion of patients with PMAs, which are tumors with the longest diameter <1 cm, 36 patients with PMA invading extrasellar areas were analyzed.

Patients were divided and analyzed according to type of tumor: fx and non-fx PMA. Although silent corticotroph pituitary adenoma (SCPA) is a non-fx subtype that demonstrates positive immunohistochemistry for adrenocorticotropic hormone without causing Cushing's disease, it is known to exhibit more aggressive behavior, compared to standard non-fx tumors.[14] Therefore, we categorized patients with SCPA into the fx tumor group.

Definition of treatment results

Tumor control was defined separately for fx and non-fx PMA. In non-fx PMA, no radiologic progression on brain MRI was the only criterion that defined tumor control.[15] In fx PMA, normalization of hypersecreted hormones, maintenance of normalized status, and lack of radiological progression were required for tumor control. An increase in tumor size on brain MRI was defined as "local failure" in both fx and non-fx tumors. A "biochemical failure" was defined in fx adenomas as a rise in serum levels of a respective hormone against a previously stable or falling value and failure to control the serum hormone level. If a patient with PMA met any of the local or biochemical failure definitions, the case was defined as "any failure."

RT for PMA

The aim of RT was categorized into three groups: salvage RT alone, immediate postoperative RT, and delayed postoperative RT. When patients received RT after tumor removal without evidence of tumor size increase on brain MRI or aggravation of clinical signs or symptoms, they were categorized into a postoperative group. Immediate postoperative RT was defined as a time interval of 3 months or less between surgical resection and RT, while delayed postoperative RT was more than 3 months. Patients who received RT without tumor removal for recurrence or size increase were classified as salvage RT.

All patients in this study were treated with a megavoltage beam linear accelerator using two-dimensional RT (2D-RT), three-dimensional conformal RT (3D-CRT), and intensity-modulated RT (IMRT) techniques. Before 2005, 2D-RT with a bilateral open field and a selective anterior beam was used. For 3D-CRT and IMRT, contrast-enhanced CT-based target delineation with the fusion of diagnostic MRI was conducted. Thermoplastic head-neck-shoulder devices were applied individually for the accurate setup and delivery of RT.

The clinical target volume (CTV) included the gross tumor and encompassing sellar area. To compensate for setup errors, a 3–5 mm margin was added to the CTV. Daily patient alignment using kilo- or mega-voltage CT was performed for IMRT cases.

Follow-up and treatment outcome evaluation

To evaluate local tumor failure, brain MRI scans were taken 3 months after RT, and were evaluated according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1). Patients were advised to undergo an MRI annually until the first 5-year follow-up visit, and every 2 years thereafter. In addition to the imaging follow up, endocrinologic evaluations of serum hormone levels were recommended every 6 to 12 months. Ophthalmologic evaluation with the visual field test was performed before and after RT. An annual ophthalmologic follow up was also recommended. RT-related toxicity

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at the time of follow-up was graded according to the Common Terminology Criteria for Adverse Events (version 5.0).[16]

Statistical analysis

Statistical analyses were conducted using IBM SPSS (version 25.0; IBM Corp., Armonk, NY, USA) and R (version 3.6.1; R Development Core Team 2009, Vienna, Austria). Local FFR, biochemical FFR, any FFR, and overall survival were estimated using the Kaplan–Meier method, calculated from the initiation of RT. To test the statistical differences between the curves, a log-rank test was used. Univariate and multivariate Cox regression analyses were conducted to identify prognostic factors of local control rates. The differences in patient characteristics were compared using chi-square tests. One-way analysis of variance was used to compare the patient characteristics across three or more groups for characteristics that were numerical variables. Statistical significance was set at $p<0.05$.

Table 1. Patient and Disease Characteristics (n=36)

Variables	Value
Age (yr)	56 (24–76)
Sex	
Male	13 (36.1)
Female	23 (63.9)
Median follow-up months	80.5 (16–259)
Type of PMA	
Functioning tumor	14 (38.9)
Non-functioning tumor	21 (58.3)
SCPA	1 (2.8)
Type of secreting hormone (n=14)	
Prolactin	6 (42.9)
Growth hormone	1 (7.1)
Adrenocorticotropic hormone	4 (28.6)
Others	3 (21.4)
Karnofsky performance score	
100	11 (30.6)
90	16 (44.4)
80	6 (16.7)
70	2 (5.6)
60	1 (2.8)
Time interval between surgical resection and RT (n=11)	
0–3 month	6 (54.5)
>3 months	5 (45.5)
Extent of disease	
Cavernous sinus invasion	27 (75.0)
Sphenoid sinus invasion	11 (30.6)
Ethmoid sinus invasion	7 (19.4)
Clivus invasion	10 (27.8)
Suprasellar region invasion	27 (75.0)
Size of tumor (cm)	3.4 (1.3–5.8)
<4 cm	22 (61.1)
>4 cm	14 (38.9)

PMA, pituitary macroadenoma; SCPA, silent corticotroph pituitary adenoma; RT, radiation therapy.
Data are presented as median (range) or n (%).

RESULTS

Patient characteristics

Characteristics of the entire study population are described in Table 1. The proportion of patients with fx adenoma was 41.7% (15/36 patients), and prolactin-producing adenoma was the most frequent. The performance status of patients was investigated and >90% of patients had an Eastern Cooperative Oncology Group score ≤1 and Karnofsky Performance Scale score ≥80. The median tumor size was 3.4 cm. The disease extent before RT was described according to the invasion of structures adjacent to the pituitary gland. Tumors invading the suprasellar area and cavernous sinus were the most frequent presentation, accounting for 75% of the cohort.

Due to the mass effect of tumors invading extrasellar structures at the time of initiation of RT, 16 (44.4%) and 13 (36.1%) patients presented with ophthalmologic problems and hypopituitarism, respectively. Ophthalmologic problems included visual field defects, blurred vision, extraocular muscle movement impairment, and diplopia. Thirteen patients with hypopituitarism were receiving hormone replacement. Other clinical presentations before RT were headache, nausea, and vomiting.

RT and treatment outcomes

Specific details of RT are shown in Table 2. Approximately 86% of patients (31/36) received CT-based 3D-CRT or IMRT. Dose prescriptions of 45 Gy in 25 fractions were the most common,

Table 2. Characteristics of RT (n=36)

Variables	Value
RT technique	
Two-dimension	5 (13.9)
Three-dimension conformal	14 (38.9)
Intensity modulation	17 (47.2)
Total RT dose	45 Gy (45.0–54.0)
Fraction size	
1.8 Gy	30 (83.3)
2.0 Gy	6 (16.7)
RT scheme	
45 Gy/25 fx	29 (80.6)
50 Gy/25 fx	5 (13.9)
50.4 Gy/28 fx	1 (2.8)
54 Gy/30 fx	1 (2.8)
RT aim	
Immediate postoperative RT	6 (14.0)
Delayed postoperative RT	5 (11.6)
Salvage RT alone	25 (58.1)

RT, radiation therapy.
Data are presented as median (range) or n (%).

accounting for 80% of prescriptions in all patients. The median intervals from surgery to RT were 1 month (range, 0–3) and 7 months (range, 6–8) for the immediate postoperative RT and delayed postoperative group, respectively.

Treatment outcomes according to tumor types are shown in Fig. 1 and Supplementary Fig. 1 (only online). The median follow-up periods (months) were 82 (range, 16–259), 79 (range, 26–259), and 82 (range, 16–232) months for overall study population, fx-adenoma, and non-fx adenoma group, respectively. The 10-year local FFRs were 100% and 74.7% in non-fx and fx PMA, respectively (p=0.047) (Fig. 1A). The 10-year biochemical FFR calculated for fx adenoma was 84.4% (Supplementary Fig. 1, only online). The 10-year any FFRs were 100% and 78.8% for fx and non-fx adenomas, respectively, and showed a significant difference (p=0.035) (Fig. 1B).

Local and any FFRs were evaluated according to RT aim (Fig. 2). In the immediate postoperative RT group, 10-year local and any FFRs were 100%; the delayed postoperative group showed the worst results, with 10-year local and any FFRs of 80% and 60%, respectively (p=0.043; p=0.022) (Fig. 2). The p values of log rank tests for local FFR were 0.312 (immediate postoperative RT vs. salvage RT group) and 0.072 (immediate postoperative RT vs. delayed postoperative RT group). FFR curves were also made for patients with fx adenoma only (Supplementary Fig. 2, only online). Although the difference in Kaplan–Meier curves of local and biochemical FFRs was more prominent than that in the whole cohort, they were not statistically significant (p=0.126; p=0.410) (Supplementary Fig. 2A and B, only online). However, there was a significant difference in any FFR according to RT aim, with 10-year rates of 100%, 33.3%, and 90% for immediate postoperative, delayed postoperative, and salvage RT groups, respectively (p=0.032) (Supplementary Fig. 2C, only online).

To identify any bias between the three RT aim groups, the patient characteristics were compared (Supplementary Table 1, only online). The median follow-up months were 84, 82, and 36 months for the salvage, immediate postoperative, and de-

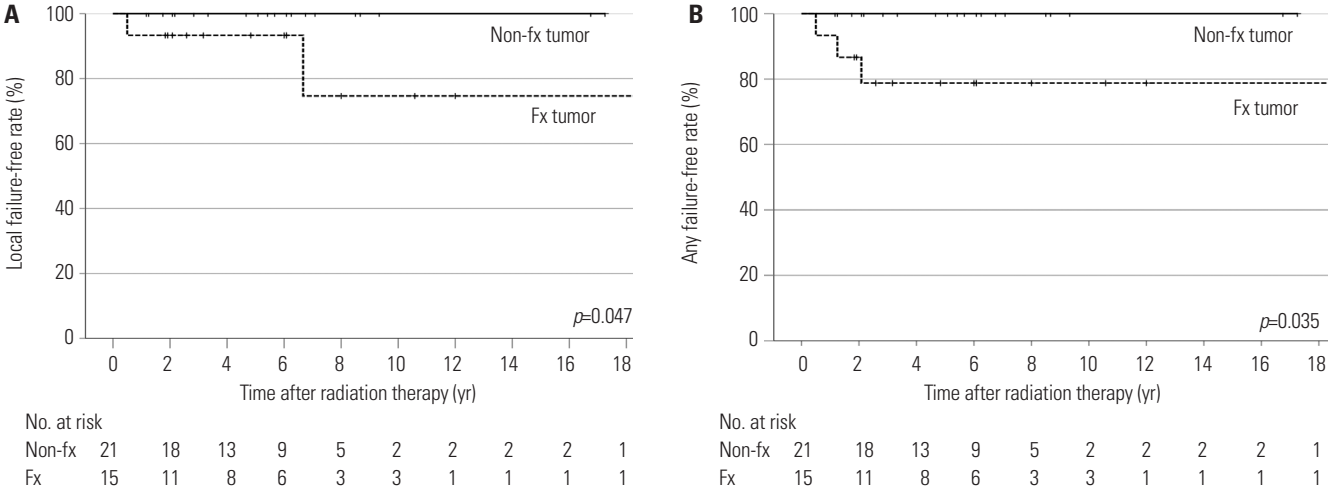

Fig. 1. (A) Local failure-free rate, and (B) any failure-free rate after radiation therapy according to the type of pituitary adenoma. Fx, functioning.

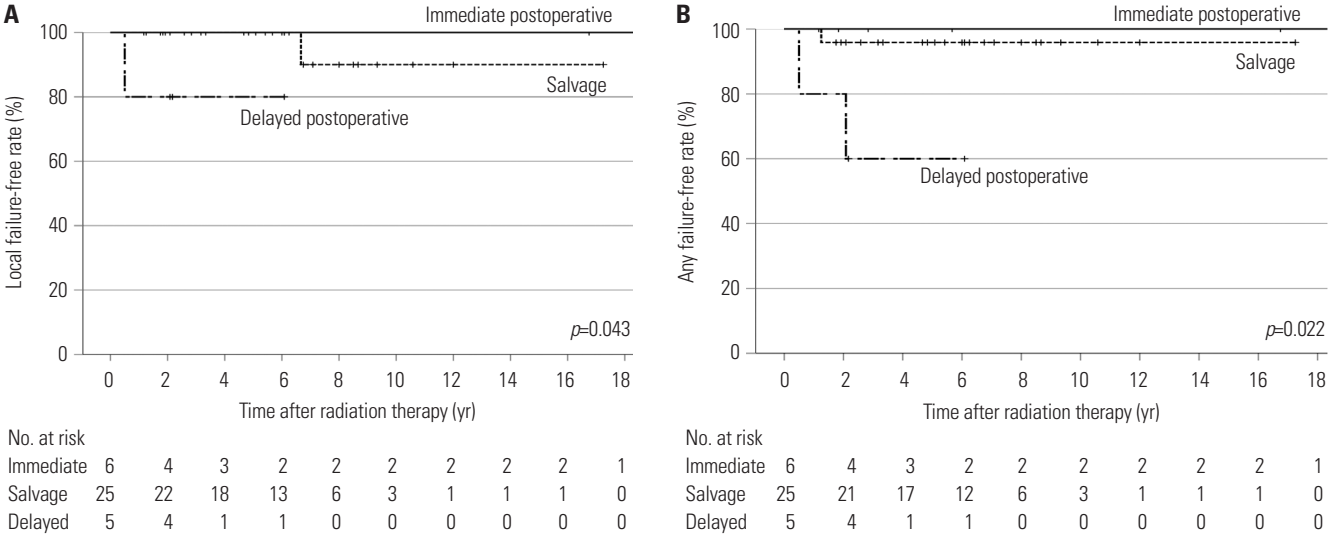

Fig. 2. (A) Local failure-free rate, and (B) any failure-free rate according to the aim of radiation therapy.

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layed postoperative groups, respectively (p=0.428). There were no significant differences in patient and disease characteristics among the three groups (p>0.05).

Among 16 patients with pre-existing visual impairment, six showed slight improvement of the visual field or subjective symptom palliation. In two patients, visual improvements were confirmed through visual field tests, while others were evaluated based on subjective reports. Only two patients were able to cease hormone replacement treatment after RT among the 13 who were being treated for hypopituitarism.

Treatment outcomes according to disease characteristics

Local FFRs according to tumor size and disease extent were calculated using the Kaplan–Meier method. The median follow-up period for <4 cm and >4 cm tumors were 92 months (range, 19–232), and 55 months (range, 16–259), respectively. The 10-year local FFRs were 100% for tumors >4 cm and 84.7% for tumors <4 cm (p=0.320) (Supplementary Fig. 3A, only online). Any FFRs according to the tumor size were not significant (p=0.820) (Supplementary Fig. 3B, only online). We also tested other cut off values of tumor size [3 cm, 3.4 cm (median tumor size of our study population), 5 cm], but there were no significant differences in local and any FFRs. The local FFRs were also compared according to the specific location of the extrasellar area that tumors invaded (Supplementary Fig. 4, only online). Patients with cavernous sinus and suprasellar area invasion had a 100% 10-year local FFR, while that of patients without invasion was 44.4% (Supplementary Fig. 4A and B, only online). Sphenoid and ethmoid sinus and clivus invasion were also not significant predictive factors for local failure, with p>0.05 (Supplementary Fig. 4C-E, only online). Ki-67 index values were available in 18 patients: 9 patients in the postoperative group and 9 patients in the salvage RT group. There were one local failure and two any failures in patients with a Ki-67 index of 1%. The incidence of local failure and any failure according to the Ki-67 index are presented in Supplementary Table 2 (only online).

We compared successful treatment and treatment failure groups to identify any radiologic or disease features associated with treatment outcomes (Table 3). Among three treatment failures, two were found in fx tumors, while there was no treatment failure among non-fx tumors (p=0.032). One local failure occurred in a patient with SCPA. Time interval between surgical resection and RT in postoperative subgroups showed borderline significance in relation to treatment failures (p=0.082). The extent of extrasellar invasion and size of the tumor were not statistically significant. In addition, we examined the results of Cox regression analysis to identify any predisposing factors for local and any failure (Table 4), and there were no statistically significant risk factors for local and any failure in univariate analysis.

Late sequelae of RT

There were no grade 3 or higher RT-related acute toxicities. The most common signs of acute toxicity were headache (grade 1,

Table 3. Patient Characteristics according to Treatment Outcome (n=36)

Variables	Treatment failure (any failure)	No treatment failure	*p* value
Age (yr)	55 (32–58)	56 (24–76)	0.466
Sex			0.917
Male	1 (33.3)	12 (36.4)	
Female	2 (66.7)	21 (63.6)	
Median follow-up months (range)	89 (36–100)	75 (16–259)	
Type of PMA			0.032
Functioning tumor	2 (66.7)	12 (36.4)	(fx vs. non-fx)
Non-functioning tumor	0 (0.0)	21 (63.6)	
SCPA	1 (33.3)	0 (0.0)	
Type of functioning tumor (n=14)			0.058
Prolactin	0 (0.0)	6 (50.0)	
Growth hormone	1 (50.0)	0 (0.0)	
Adrenocorticotropic hormone	1 (50.0)	3 (25.0)	
Others	0 (0.0)	3 (25.0)	
Karnofsky performance score			0.248
100	1 (33.3)	10 (30.3)	
90	0 (0.0)	16 (48.5)	
80	1 (33.3)	5 (15.2)	
70	1 (33.3)	1 (3.0)	
60	0 (0.0)	1 (3.0)	
Time interval between surgical resection and RT (n=11)			0.087
0–3 months	0 (0.0)	6 (66.7)	
>3 months	2 (100.0)	3 (33.3)	
Extent of disease			
Cavernous sinus invasion			0.082
Yes	1 (33.3)	26 (78.8)	
No	2 (66.7)	7 (21.2)	
Sphenoid sinus invasion			0.913
Yes	1 (33.3)	10 (30.3)	
No	2 (66.7)	23 (69.7)	
Ethmoid sinus invasion			0.526
Yes	1 (33.3)	6 (18.2)	
No	2 (66.7)	27 (81.8)	
Clivus invasion			0.822
Yes	1 (33.3)	9 (27.3)	
No	2 (66.7)	24 (72.7)	
Suprasellar region invasion			0.002
Yes	0 (0.0)	27 (81.8)	
No	3 (100.0)	6 (18.2)	
Size of tumor (cm)	2.9 (1.5–5.3)	3.6 (1.3–5.8)	0.112
<4 cm	1 (33.3)	13 (39.4)	0.805
>4 cm	2 (66.7)	20 (60.6)	

PMA, pituitary macroadenoma; RT, radiation therapy; SCPA, silent corticotroph pituitary adenoma.
Data are presented as median (range) or n (%).

Table 4. Univariate Analysis Conducted with a Cox Regression Model of Patient Characteristics and Local Failure/Any Failure

Variables	Univariate analysis		
	HR	95% CI	*p* value
Local failure			
Age	0.928	0.830–1.038	0.181
Sex (male vs. female)	2.974	0.169–52.238	0.465
Type (functioning vs. non-functioning)	96.366	0.001–1.1*10^{7}	0.443
Tumor size (<4 cm vs. >4 cm)	39.613	0.00–1.1*10^{8}	0.564
Karnofsky performance score	0.985	0.92–1.054	0.657
RT dose (45 Gy vs. ≥50 Gy)	0.037	0.00–2.1*10^{6}	0.677
Suprasellar invasion (yes vs. no)	0.001	<0.01–3.2*10^{7}	0.537
Ethmoid invasion (yes vs. no)	0.037	0.00–2.1*10^{6}	0.677
Sphenoid invasion (yes vs. no)	0.030	0.00–1.5*10^{4}	0.599
Cavernous invasion (yes vs. no)	0.001	0.00–3.2*10^{7}	0.537
Clivus invasion (yes vs. no)	0.031	0.00–1.9*10^{4}	0.609
Ki-67 index	0.400	0.026–6.10^{4}	0.510
RT aim (immediate postoperative vs. salvage/delayed postoperative RT)	0.038	0.00–3.7×10^{6}	0.690
Any failure			
Age	0.951	0.868–1.041	0.275
Sex (male vs. female)	1.147	0.104–12.657	0.911
Type (functioning vs. non-functioning)	104.741	0.007–1.5*10^{7}	0.344
Tumor size (<4 cm vs. >4 cm)	1.340	0.121–14.806	0.811
Karnofsky performance score	0.992	0.945–1.041	0.737
RT dose (45 Gy vs. ≥50 Gy)	0.471	0.192–23.447	0.540
Suprasellar invasion (yes vs. no)	0.001	0.00–8.3*10^{9}	0.427
Ethmoid invasion (yes vs. no)	0.471	0.043–5.210	0.540
Sphenoid invasion (yes vs. no)	0.864	0.078–9.547	0.905
Cavernous invasion (yes vs. no)	0.160	0.567–69.053	0.134
Clivus invasion (yes vs. no)	0.743	0.067–8.224	0.809
Ki-67 index	0.417	0.066–2.622	0.351
RT aim (immediate postoperative vs. salvage/delayed postoperative RT)	0.038	0.00–2.5*10^{4}	0.632

HR, hazard ratio; CI, confidence interval; RT, radiation therapy.
Data are presented as median (range) or n (%).

7 patients) and nausea or vomiting (grade 1, 6 patients), and all were self-limiting. Seven patients had newly developed hypopituitarism and none developed visual impairment as late toxicities of RT. Secondary intracranial tumors, including glioma, sarcoma, and meningioma, were not detected in any patients during the follow-up period.

Representative cases

A 53-year-old female visited the clinic with symptoms of repeated epistaxis and rhinorrhea (Fig. 3A). In a brain MRI, a 5.1-cm pituitary tumor invading the bilateral cavernous sinus, clivus, and left ambient cistern was found without any visual or endocrinologic impairment. Surgical removal through the TSA approach failed to achieve complete resection, and the residual tumor extent was almost the same as that before surgery. The tumor was identified as a non-fx PMA via a pathologic review. RT with 45 Gy in total, with 1.8 Gy per fraction, was delivered using IMRT after 4 weeks of the TSA. Consecutive MRIs after RT are shown in Fig. 3A, and no residual tumors were detected after 6 years of follow-ups. There were no signs of acute toxicity during or after RT. As of the last follow-up, the patient showed no hypopituitarism or visual discomfort as late toxicities of RT.

Surgical resection with immediate postoperative RT for recurrent PMA resulted in long-term local and biochemical control in a 48-year-old female patients with an fx tumor (Fig. 3B). The recurrent prolactin-secreting PMA, located in the sellar region, compressed the optic chiasm and had invaded the suprasellar area and right cavernous sinus. The patient had a history of TSA as a primary treatment for pituitary tumor, and surgical resection induced panhypopituitarism and underlying bilateral temporal quadrantanopia. The recurrent tumor was treated with subtotal tumor resection and immediate postoperative RT. There was no tumor progression or newly developed RT-related toxicity during the follow-up period, which lasted more than 15 years.

DISCUSSION

We evaluated the treatment results of recurrent or residual PMAs invading extrasellar structures after conventional fractionated RT. The local control rate of tumors was comparable to those of non-recurrent or non-aggressive tumors. A fx adenoma was the only significant characteristic that led to a worse local control rate; while size of tumor and location of extrasellar area that tumor invades were not prognostic for treatment failure, which is not consistent with other previous studies. The unique point to our study is that patients who received immediate postoperative RT showed better treatment outcomes, compared to delayed postoperative RT, suggesting a hypothesis that immediate postoperative RT can contribute towards a better local FFR in patients with recurrent or residual PMA. Although the interpretation of our results requires special consideration due to the small number of study participants and failure events, we believe our study may spur further studies with a larger number of patients to evaluate the predisposing factors of treatment failure after RT in residual or recurrent PMA.

For recurrent or residual PMAs, secondary surgical resection is commonly performed as a salvage treatment. However, total resection rates are known to be lower than those of tumors confined within the sellar area, with an increased risk of resection-related acute toxicities. Therefore, the application of RT or stereotactic radiosurgery (SRS) for PMAs invading extrasellar structures has been continuously increasing, with favorable treatment results.[17] Sheehan, et al.[13] reported tumor control rates of over 95% after gamma knife surgery (GKS) with a mean RT dose of 16 Gy. Conventional fractionated RT for large residual tumors was also effective in tumor control with a

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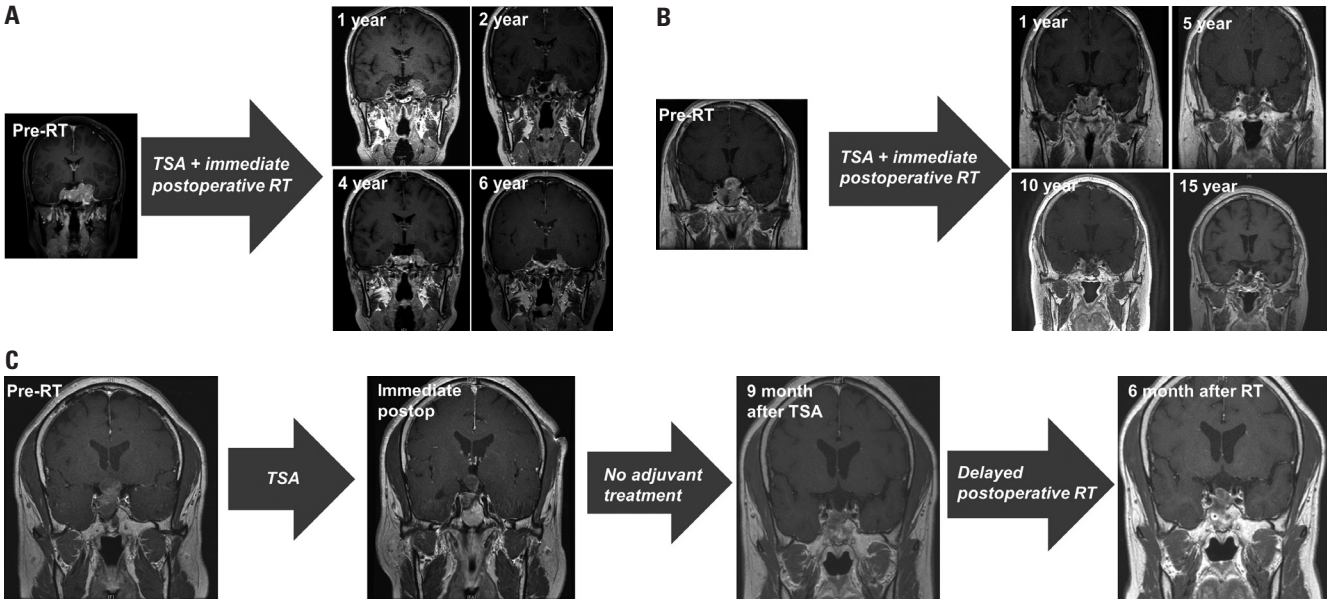

Fig. 3. Representative cases of our study. (A) and (B) demonstrate favorable treatment outcomes after immediate postoperative RT for recurrent nonfunctioning and functioning pituitary adenomas, respectively. (C) Shows local failure after six months of RT in a patient with a silent corticotroph pituitary adenoma. RT, radiation therapy.

10-year control rate of 91%.[18] Both SRS and conventional RT are viable treatment options, and the treatment results are expected to be comparable for both.[19] The Congress of Neurological Surgeons guidelines recommend conventional RT over SRS for operative residues to reduce the risk of tumor progression.[12] Guidelines from the European Society of Endocrinology for the management of aggressive pituitary tumors also recommend adjuvant RT for initial postoperative residuum with clinical indicators, such as high Ki-67 or invading extrasellar structures.[13] However, current guidelines are based on evidence levels 2 and 3, and further investigations are needed to define the effectiveness of RT as a treatment option for residual or recurrent PMA.[20]

Patients with PMA invading extrasellar structures frequently present with mass-induced symptoms, such as hypopituitarism or visual disturbances. Therefore, control of tumor growth through local treatment to prevent any further aggravation of symptoms is important. RT is an attractive treatment method for local control of extrasellar PMAs; however, the use of RT must be weighed against risks. To decrease the possibility for toxicities after RT exposure, several efforts have been made to identify patients at greater risk of tumor progression who would benefit from RT. The 2017 WHO classification of pituitary tumors defined aggressive adenomas as a combination of tumors with atypical histomorphological features and special subtypes and clinical parameters, such as tumor invasion.[21] Invasion of the cavernous sinus, clivus bone, or sphenoid bone is thought to be a possible marker of aggressive pituitary adenoma.[20] Our study investigated the effects of RT in PMAs with aggressive features, targeting patients with tumors invading extrasellar structures: tumor control rates were comparable to those in several other studies with non-aggressive features. The extent of extrasellar tumor invasion and tumor size were not predictive factors for local tumor growth, and RT was successfully used to control the tumors. In our study, immediate postoperative RT was effective for local tumor control, although the timing of RT has not yet been fully investigated as a prognostic factor. Pomeraniec, et al.[22] reported a statistically greater risk of tumor progression in patients treated with late GKS (>6 months; p=0.027), with a median follow-up period of 68.5 months. However, the data were insufficient to conclude whether earlier RT would induce better tumor control and requires further investigations. A huge adenoma ≥4 cm, which is the most commonly used criterion to define giant pituitary adenoma,[23] was also not a prognostic factor in predicting local failure, and the type of tumor was only a predictive factor for local tumor control.

Our study included one case of variation, which was an SCPA (Fig. 3C). After surgical resection of the recurrent tumor, the residual tumor remained in the sellar and cavernous sinus areas. At 9 months after a TSA, delayed postoperative RT was delivered for the residual tumor and sellar area with 45 Gy in 25 fractions. However, local progression in the suprasellar area was detected by MRI after 6 months of RT. As a distinct type of pituitary adenoma, SCPA is known to show more aggressive features than other non-fx tumors.[14,24,25] However, due to the rarity of SCPA, accounting for 5.5% of all non-fx PMAs, objective treatment strategies are not well established, and there remain discrepancies between reported studies.[26] In a recent retrospective study,[14] SCPAs had significantly lower progression-free survival than other non-fx tumors (24.5 months vs. 51.1 months, p=0.001). Furthermore, immediate adjuvant SRS was unsuccessful in delaying the time to progression after subtotal resec-

tion of tumors, while some have shown a decline in recurrence rates following adjuvant RT.[25,27] In addition to the traditional classification of pituitary tumors, the 2017 WHO classification emphasized immunologic expression, such as T-pit genes, to understand the disease in depth.[28] Studies dealing with specific genetic expression should be performed with larger number of study patients.

The choice of RT modality largely depends on the distance from critical normal structures. SRS is considered an attractive option over fractionated RT, as it is usually a single fraction treatment. For non-fx tumors, one study reported a recurrence rate of 9.6% after SRS treatment, with a median 78-month follow up.[29] The rates of biochemical remission after SRS are known to below. The average biochemical remission rate for growth hormone-secreting tumors was 48% at 5 years. In patients with Cushing's disease, the biochemical remission rate was 64% across 15 studies with 465 patients.[30] Conventional RT and SRS showed similar rates of hormonal remission in a recent meta-analysis, indicating that the toxicity of RT is a major factor in selecting the modality.[31] The risk of optic neuropathy varies from 1%–5% after conventional RT to 1%–4% after SRS, when the dose to the optic pathway is less than 10 Gy.[32] However, tumors invading extrasellar structures, particularly the suprasellar area, tend to be located near the optic chiasm or optic pathways, and meeting the dose constraints for such tumors can be difficult. One study evaluated the efficacy of debulking surgery for pituitary adenomas located <2 mm from the optic chiasm to facilitate SRS, in which only 29% (9/31 patients) were classified as SRS candidates.[33] Therefore, fractionated conventional RT might be the inevitable option in such cases to safely preserve the optic pathways from possible radiation damage, and our study showed promising results with comparable tumor control rates and tolerable toxicities.

To reduce the toxicity of RT, pituitary tumor was one of the first candidates for high-energy proton beam therapy (PBT). Following the first report on proton beam therapy in acromegaly in the 1960s,[34] recent multiple series have reported PBT as an alternative to fractionated RT or SRS, with a lower risk of toxicities.[35] Ronson, et al.[36] reported tumor regression or stabilization in all patients after fractionated PBT with 1.8 or 2 cobalt grey equivalent daily fractions. However, hypopituitarism as a complication of RT was noted for 20% and 35% of non-secreting and secreting adenomas, respectively. Furthermore, seven of 43 patients (23.3%) reported new visual deficits, two of which were major: right. quadrantanopia and visual loss. The reported toxicity rates seemed much higher than conventional fractionated RT or SRS. It is also not clear whether PBT would be safe in treating PMAs with invading extrasellar areas. In a recent dosimetric comparison study from Harvard, a PBT successfully reduced the maximum dose and equivalent uniform dose to critical proximal structures, such as optic pathways.[37] Even though its dosimetric superiority is preferential in saving critical normal organ structures, further clinical studies are required to assess whether PBT elicits a lower incidence of toxicities, such as hypopituitarism or optic pathway damage.

Our study has some limitations. First, we were unable to analyze the treatment results according to the latest WHO classification of pituitary tumors. Considering the nature of benign tumors, a sufficient follow-up duration after treatment is mandatory for the accurate evaluation of treatment results; therefore, patients who were treated more than a decade ago were included as a target of the study. Consequently, molecular expressions such as pituitary-specific positive transcription factor 1 or steroidogenic factor 1, could not be analyzed in our study. Second, signs of toxicity of RT, including hypopituitarism or visual impairments, could have been underestimated due to a considerable rate of patients already having these clinical presentations as an underlying condition. Third, relative small numbers of patients and events of treatment failure were analyzed in the study, making overfitting of the Cox regression model a concern. Consequently, we were not able to suggest informative multivariate analysis. Further studies with a larger number of patients and sufficient follow up period are expected to clearly demonstrate the risk factors of treatment failure in recurrent or residual PMAs. At last, there was no secondary malignancy development after RT in our study population, and this might have been derived from relatively short term follow-up period. A recent multicenter retrospective study with more than 3500 patients of pituitary adenoma and craniopharyngioma reported that older age at pituitary tumor detection and exposure to RT were associated with a higher risk of secondary brain malignancy.[38] Although the 20-year cumulative incidence of secondary brain tumor in irradiated patients was only 4.0%, it was significantly higher than 2.1% in the non-irradiated control group (p=0.030). For patients who are expected to survive more than several decades, the increased risk of secondary malignancy at an irradiated area should warrant concern despite a very low absolute incidence.

In conclusion, conventional fractionated RT for PMA invading extrasellar structures achieved local tumor control results that were comparable to other tumors with non-aggressive features. The extent of tumor invasion was not a predictive factor of local control. The results of our study suggest that immediate postoperative RT can be beneficial to delayed postoperative RT or salvage RT. Further studies with a larger number of patients to evaluate the risk factors of treatment failure regarding treatment and disease characteristics are warranted.

DATA AVAILABILITY STATEMENT

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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